Renal Transplantation in HIV-Infected Patients: The First Portuguese Review

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ABSTRACT

Introduction. With the introduction of combination antiretroviral therapy (cART), prognosis of human immunodeficiency virus (HIV) infection has been improved and kidney transplantation (KT) in HIV-positive patients became possible.

Methods. We reviewed the demographic, clinical, laboratory, and therapeutic data of all the HIV-infected patients who underwent KT between 2009 (first KT in Portugal in a HIV-infected patient) and May 2014. Case accrual was through all Portuguese KT centers where a KT in an HIV-infected patient was performed. Patients were transplanted following the American and Spanish guideline recommendations that included maintenance on cART, undetectable plasma HIV RNA copies, and absolute CD4 counts of $\geq$200 cells/μL in the last 6 months.

Results. Fourteen KT were performed on men and 3 on women. The mean age of patients at the time of transplantation was 49.9 $\pm$ 11.7 years. HIV status was known for 12 $\pm$ 5 years. Eight patients had AIDS in the past and all patients received grafts from deceased donors. Twelve patients (64.7%) underwent induction therapy with basiliximab and 2 patients experienced early graft loss. In 2 patients, humoral rejection was diagnosed and in 3 patients, cellular rejection. Two patients died and an additional patient had early graft loss.

Conclusion. KT is a possible, but challenging, renal replacement therapy in selected HIV-positive patients. Even in those with AIDS criteria in the past, when the disease is controlled, and after the reconstitution of the immune system with cART, KT can be performed. Nevertheless, the risk–benefit ratio for each patient needs to be taken in consideration.

WITH THE INTRODUCTION of combination antiretroviral therapy (cART) in 1996, prognosis of human immunodeficiency virus (HIV) infection has improved owing to a sustained suppression of HIV replication and immunologic recovery and the risk of opportunistic infections became very low [1,2]. Therefore, kidney transplantation (KT) became possible in HIV-positive patients. In the United States and Europe, approximately 1%–1.5% of patients with end-stage renal disease (ESRD) are infected with HIV [3,4]. In January 2014, 151 HIV-positive patients were undergoing dialysis in Portugal and 9 of these patients were on a waiting list for KT [5].

Several scientific societies have developed guidelines regarding organ transplantation in these patients. The candidate for KT should not suffer from any condition included in category C that define AIDS, CD4 lymphocyte count should be >200 cells/μL, and HIV viral load should be undetectable [6,7] for a period of $\geq$6 months. Social and psychiatric evaluations must be done and, usually, in drug abusers, a period of abstinence of >2 years is recommended.

Furthermore, although the frequency of AIDS defining events has decreased, non–AIDS-related events, including ESRD, has increased. HIV-infected patients may suffer

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Table 1. Demographic and Clinical Data From HIV-Positive Recipients

Patient	Gender	Age	HIV Diagnosis (year)	Rejection	Coinfection	Follow-up After KT (mo)	CrCL MDRD (mL/min/1.73 m^2) 6/12/24/36 mo	Graft Loss/Patient Death
1	M	57	1998	AHR	BK	34	36/33/31/–	No
2	M	51	2002	No	No	21	83/95/–/–	No
3	M	66	1999	No	No	14	53/49/–/–	No
4	M	43	1987	No	No	16	54/60/–/–	No
5	M	66	1998	No	No	3	–	No
6	F	35	1996	No	No	3	–	No
7	M	38	1994	No	HCV	0	–	Death/graft loss: hypovolemic shock
8	M	65	2003	No	No	0	–	Graft loss: vascular thrombosis
9	M	32	2009	No	No	15	35/63/–/–	No
10	M	65	2003	AHR	No	8	53/–/–/–	No
11	F	48	2005	ACR	No	6	76/–/–/–	No
12	M	56	1999	ACR	No	3	–	No
13	M	44	2005	ACR	No	52	75/43/58/49	No
14	M	45	2000	No	No	42	91/66/72/88	No
15	F	58	2003	No	No	24	63/61/52	No
16	M	47	2002	No	No	21	91/94/–/–	No
17	M	64	2006	No	No	2	–	Death: H1N1 infection

Abbreviations: ACR, acute cellular rejection; AHR, acute humoral rejection; CrCL, creatinine clearance; F, female; HCV, hepatitis C virus; HIV, human immunodeficiency virus; M, male; mo, months; MDRD, Modification of Diet in Renal Disease.

from kidney failure owing to usual causes of ESRD or directly owing to HIV infection, including HIV-related nephropathy (HIVAN), immune complex–mediated glomerulonephritis, and thrombotic microangiopathy [8]. Additionally, HIV-infected patients may suffer kidney injury through complications of infection or nephrotoxicity of antiretroviral therapy [9].

In our study, we evaluated the characteristics and evolution of all patients who received a renal allograft in Portugal between 2009 and May 2014.

METHODS

We reviewed the charts of all HIV-infected patients who had undergone KT between 2009 (first KT in Portugal in a HIV-infected patient) and May 2014. We analyzed HIV subtype, evolution of the viral disease, etiology of the renal disease, diabetes, time on dialysis, immunologic compatibility, coinfection with cytomegalovirus and BK, immunosuppression and antiretroviral therapies before and after KT, rejection episodes, graft function, and graft and patient survival. Renal function was expressed as estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistics

Statistical parameters were calculated using Microsoft Office Excel 2011 and were used the following parameters: percentage, average, or standard deviation.

RESULTS

We identified 17 KT in 16 different patients (1 re-KT). Six KT were performed in Hospital de Santa Cruz, 6 KT (in 5 patients) in Hospital Curry Cabral, 4 KT in Hospital de São João, and 1 KT in Hospital Garcia de Orta, which was the first performed in Portugal, in November 2009.

Of 17 KT, 14 were performed in men. The mean age of patients at the time of transplantation was 49.9 ± 11.7 years; 10 patients were Caucasian and 14 KT were performed on HIV type 1 patients; 2 patients were HIV type 2 positive [10]. HIV status was known for 12 ± 5 years; the HCV co infection rate was 11.8% (2/17). Four patients had HIVAN, 2 patients had autosomal-dominant polycystic kidney disease. The other 3 had immunoglobulin (Ig)A nephropathy, diabetic nephropathy, and chronic glomerulonephritis. The etiology was uncertain in 8 patients whom had only known their kidney disease already in stage 5, precluding a histologic diagnosis. The median time on dialysis was 115.8 ± 65.7 months; 8 patients had previously fulfilled diagnostic criteria for AIDS in the past. However, AIDS criteria were not present for the 6 months before KT. Only 1 patient was not taking cART therapy before KT, but he started antiretroviral treatment after receiving the allograft. Five patients were under antiretroviral protocols that included ritonavir-boosted protease inhibitors. Undetectable viral load and a CD4 lymphocyte count of ≥200 cells/μL were obtained in all recipients. All patients received grafts from deceased donors. All recipients and all donors had anti-cytomegalovirus IgG antibodies; 14 patients had >3 HLA mismatches with the donor and in 2 patients anti-HLA class I and II antibodies were identified. Six patients had a panel reactive antibody of >25%. Twelve patients (64.7%) received induction therapy with basiliximab, 3 patients with polyclonal antibodies and 1 patients received rituximab and intravenous immunoglobulin (IVIg). Fifteen patients received triple maintenance immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and a corticosteroid. Two patients had an early graft loss, one owing to hypovolemic shock at the day 4 after KT, the other owing to vascular thrombosis at day 4 after KT. Two patients died, one owing to hypovolemic shock at day 4 after KT, and other at 2 months after KT, with a

functioning graft, owing to H1N1 infection. One patient has been coinfected with polyomavirus BK 4 months after KT and his immunosuppressive regimen was changed to sirolimus, tacrolimus, and prednisone.

All recipients under antiretroviral therapy were maintained on previous cART; the patient who had never been under antiretroviral therapy before KT started cART after the procedure. All 5 patients who were under ritonavir-boosted protease inhibitors remained on this drug regimen. However, it was necessary to reduce substantially the dose of tacrolimus to achieve therapeutic range.

Humoral rejection was detected in 2 patients and cellular rejection in 3. The 3 patients with acute cellular rejection were treated with steroid pulses, with recovery of previous renal function. The 2 patients with acute humoral rejection were treated, 1 with plasmapheresis, rituximab, and IVIg, and the other with thymoglobulin, plasmapheresis, and IVIg. The first developed an acute humoral rejection episode after a significant reduction in the immunosuppression, in the context of coinfection with polyomavirus BK. Both cases of humoral rejection recovered the previous eGFR. At the date of last follow-up, average time after KT was 17 ± 14 months. The last eGFR were 64.58 ± 22.34 mL/min/1.73 m^2. We summarize the results in Table 1.

DISCUSSION

Given the increased life expectancy since the introduction of cART, HIV-positive patients develop long-term complications, such as ESRD. In the United States and Europe, 1%–1.5% of patients with ESRD are infected with HIV [3,4] and most of them are on dialysis owing to HIVAN. HIVAN is considered less common in Europe than in the United States. In our series, 4 patients (23.5%) had HIVAN diagnosed as the cause of their ESRD. We cannot exclude that HIVAN could be the cause of the ESRD of the patients whose etiology was undetermined.

The prevalence of HCV infection in HIV-infected populations is high [11]. Coinfection with HCV was been described as a negative graft survival factor, possibly owing to longer times on dialysis and duration of HIV infection. Although the evolution of HCV may be more aggressive in HIV-positive patients, KT in patients simultaneously positive for HCV and HIV infection has shown better results than dialysis [12,13]. In our case, the HCV coinfection rate was 11.8%, lower than the prevalence shown in some published literature [12].

Induction and maintenance therapy in HIV positive patients varies in different series [12–16] and raises some challenging questions. Several antiretrovirals are metabolized through cytochrome P450 (CYP450) and they may affect the function of this hepatic enzyme and P-glycoprotein (PGP) in the bowel. Ritonavir is used to boost protease inhibitors and is a potent CYP450 and PGP inhibitor. Calcineurin inhibitors and mammalian target of rapamycin inhibitors are metabolized in the liver through the CYP450 enzymatic system. Thus, the interactions between the 2 drugs lead to extremely high immunosuppressant levels. The use of integrase inhibitor-based regimens, such as raltegravir, may be useful to avoid those interactions.

The majority of our patients (94.1%) received induction therapy, 70.5% of them with basiliximab and 29.5% with thymoglobulin. In the United States, 83% of patients received induction therapy, 51% of them with anti-CD25 [15]. In a French series, 100% of patients received induction therapy [16]. All patients of our series received triple maintenance immunosuppressive therapy, which included tacrolimus. The 5 patients who were receiving ritonavir-boosted protease inhibitors, maintained this drug, however, with the need to drastically reduce the dose of tacrolimus.

We report a rate of AR of 29.4%, slightly lower than that reported in the literature [12,13,15,16]. The European and US studies describe a 1-year graft survival between 90.4% and 98% [12,15,16]. We had 2 cases of early graft loss, with a 1-year graft survival of 88.25%, equal to the patient survival. In our series, follow-up was 17 ± 14 months, which is insufficient to accurately estimate graft survival. These data reflect the Portuguese experience and are consistent with the literature results.

In conclusion, as in other series, KT seems to be an acceptable alternative to dialysis in selected HIV-positive patients, even in those with AIDS criteria in the past; however, high rejection rates can be expected. When the disease is controlled, and after the reconstitution of the immune system with cART, KT should be considered according to the risk–benefit ratio for each patient.

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